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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/012,904	01/23/1998	HARRY MEADE	TCI-028DV	2693

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EXAMINER

QIAN, CELINE X

ART UNIT	PAPER NUMBER
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1636

26

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/012,904

Applicant(s)

MEADE ET AL.

Examiner

Celine X Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19,21-23 and 25-30 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 19,21-23 and 25-30 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) ____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____

DETAILED ACTION

Claims 19, 21-23 and 25-30 are pending in the application.

This Office Action is in response to the Amendment filed on 6/17/03.

Response to Amendment

The objection to claims 29 and 30 has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 19, 21-23 and 25-30 under 35 U.S.C. 103 (a) is maintained for reasons set forth of the record mailed on 12/17/02 and further discussed below.

Response to Arguments

Claims 19, 22, 23, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97).

In response to this rejection, Applicants argue that the cited reference fails to recognize any need of combining the teaching to reach the claimed invention. Applicants further argue that Meade et al. fails to teach a) expressing light chain and heavy chain of the immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors; b) use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk; c) a unique restriction site between promoter and the 3' non-coding sequence, wherein the immunoglobulin sequence is inserted into the restriction site; d) a unique restriction site in the construct; and e) the advantage of having the unique restriction site within the construct. Applicants further argue that DeBoer et al. fails to teach these deficiencies. Applicants thus conclude that the prior art does not render the invention obvious.

The above arguments has been fully considered but deemed unpersuasive. The claimed invention is obvious in view of the combined teaching of Meade et al. and DeBoer et al. for reasons discussed in detail in the previous office action. The alleged deficiencies of a) and b) are not limitations of claims 19, 22, 23 and 25-28. Applicants are reminded although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). These claims do not recite the limitation of expressing light chain and heavy chain of the immunoglobulin separately. Contrary to Applicants' assertion that DeBoer et al. do not teach a unique restriction site in between a mammary gland promoter and 3' non-coding sequence, DeBoer et al. indeed teach such limitation. Applicants attention is directed specifically to Col.30, lines 45-50, and Figure 7E, for example, the restriction site Xho I is in between the bovine α S1 casein promoter and the 3' non-coding region. Since Meade et al. already teach a construct for expressing heterologous proteins including immunoglobulin (see col.3, lines 38-39) in mammalian milk, addition of a unique restriction site in between promoter and 3' non-coding region for addition of sequence encoding protein such as disclosed by DeBoer et al. is routine experimentation in the field of molecular cloning. One of ordinary skill in the art would have been motivated to provide such modified vectors to obviate any undesirable cleavage of the cDNA inserts which intrinsically contain common restriction endonuclease recognition sites. As methods of modifying DNA constructs are well established in the molecular biology art for the purpose of obtaining constructs with desired properties, such as tissue specific expression, and ease of insertion of various cDNAs of interest, one of ordinary skill in the art would have had a high expectation of successfully modifying the disclosed DNA constructs to obtain a DNA construct

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with tissue specificity, and a site for insertion of a desired cDNA into the vector without undue experimentation barring evidence to the contrary. Therefore, the claimed invention would have been obvious to one of ordinary skill of art at the time the invention was made.

Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., taken with DeBoer et al., (as applied to claims 19, 22, 23, and 25-28), in further view of Vandamme et al.

In response to this rejection, Applicants argue that the *in vitro* culture system taught by Vandamme et al. cannot serve as an accurate approximation of mammary gland milk synthesis of immunoglobulin assembly in whole animal. Particularly, Applicants assert that no one has established an *in vitro* system where the rates of synthesis of milk components proteins even closely approximate those found *in vivo*, hence, the two systems are incompatible and they are non-analogous art. Further Applicants assert that Vandamme references does not teach production of antibody in whole animal system, the physiological effect of lactation hormones, and milk promoters. Applicants thus conclude that the Vandamme reference teaches away from the methods required to achieve success in the expression of immunoglobulins of interest in the milk of transgenic animals.

Such arguments have been fully considered but deemed unpersuasive. Contrary to Applicants' assertion that Vandamme et al. is non-analogous art, Vandamme et al. is relevant to the claimed invention because it teaches production of recombinant immunoglobulin although the production system may be different. This case is different from the Wang case discussed by Applicants in which the memory between the references and patents has different functions and

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are used in different context. Similarly, an apparatus in which film is transferred to a welding station and a tape-silencing machine capable of handling the same film are two different devices with distinct function. Therefore, the application of King and Wang case is irrelevant to the current situation. Although Vadamme et al. do not teach production of immunoglobulin in a whole animal system, the consideration of physiological effect of lactation hormones, milk promoters, such information is taught in the primary reference Meade et al. As a secondary reference, Vadamme et al. teach the construction of a recombinant murine monoclonal antibody directed against human fibrin fragment D by co-express plasmids comprising cDNA encoding immunoglobulin light chain and heavy chain separately. With combined teaching of Meade et al. and DeBoer et al., one of ordinary skill of art would have reasonable expectation of success to use a milk specific promoter and 3' non-coding sequence to replace the regulatory sequence taught by Vadamme et al. for preferential expression of the immunoglobulin in epithelial cell *in vivo*. The difference in the rate of synthesis between *in vitro* and *in vivo* is not relevant to the claimed invention because the claims do not recite such limitation. Therefore, claims 29 and 30 are obvious in view of cited references.

Claims 19, 21-23 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97, effective filing date of 11/27/90) as applied to claims 19, 22, 23, and 25-28 above, and further in view of Bischoff et al. (FEBS Letters, 305:265-268, 1992), Buhler et al. (Bio/Technology, 9: 835-838, 1991), Gordon et al. (Bio/Technology, 5: 1183-1187, 1987), Ebert et al. (Bio/Technology, 8: 140-143, 1990), and Stinnakre et al. (FEBS Letters, 284:19-22, 1991).

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In response to this rejection, Applicants argue that none of the references cited makes up for the deficiencies as discussed above. Applicants argue that the references do not knowingly suggest the combination of protocols, test, or principles that lead to the invention to be rendered obvious. Applicants thus conclude that the motivation for combining the references is based on hindsight reasoning.

The above arguments has been fully considered but deemed unpersuasive. As discussed in the previous office action and above, the combined teaching of Meade et al. and DeBoer et al. render claims 19, 22, 23, and 25-28 obvious. Therefore, no deficiencies has to be made up by the teaching of Bischoff et al., Buhler et al., Gordon et al., Ebert et al., and Stinnakre et al. for these claims. These references teach milk specific promoters that can be used in production of heterologous proteins in transgenic mammalian milk. Therefore, claim 21 is obvious because of combined teaching of Meade et al., DeBoer et al., in further view of Bishoff et al., Buhler et al., Gordon et al., Ebert et al. or Stinnakre et al.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As such, the reference does not have to knowingly suggest the combination of protocols, test, or principles that lead to the invention to be rendered obvious, so long as the combined references provide motivation to combine and reasonable success to

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achieve the claimed invention. Such reasons for obviousness were discussed in detail in previous office action. Therefore, the rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

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Celine Qian, Ph.D.